# Region and task-specific activation of Arc in primary motor cortex of rats following motor skill learning

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# Region and task-specific activation of Arc in primary motor cortex of rats following motor skill learning

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**Running Head**: Arc induction by motor learning

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## Abstract

~~Motor~~ Motor learning requires protein synthesis within primary motor cortex (M1). Here, we show that the immediate early gene *Arc*/*Arg3.1* is specifically induced in M1 by learning a motor skill.

*Arc* mRNA was quantified using a fluorescent in situ hybridization assay in adult Long-Evans rats learning a skilled reaching task (SRT), in rats performing reaching-like forelimb movement without learning (ACT) and in rats that were trained in the operant but not the motor elements of the task (controls). Apart from M1, Arc expression was assessed within the rostral motor area (RMA), primary somatosensory cortex (S1), striatum (ST) and cerebellum.

In SRT animals, *Arc* mRNA levels in M1 contralateral to the trained limb were 31% higher than ipsilateral~~ly~~ ($p<0.001$), 31% higher than in the contralateral M1 of ACT animals ($p<0.001$) and 48% higher than in controls ($p<0.001$). *Arc* mRNA expression in SRT was positively correlated with learning success between two

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sessions (r=0.52; p=0.026). For RMA, S1, ST or cerebellum no significant differences in *Arc* mRNA expression were found between hemispheres or across behaviors.

As *Arc* expression has been related to different forms of cellular plasticity, these findings suggest a link between M1 *Arc* expression and motor skill learning in rats.

~~learning requires protein synthesis within primary motor cortex (M1). The proteins expressed to mediate successful learning are largely unknown. Here, we show that the immediate early gene *Arc/Arg3.1* is specifically induced within the caudal motor cortex (M1) by learning a motor skill.~~

~~*Arc* mRNA was quantified using a fluorescent in situ hybridization assay (FISH) in adult Long-Evans rats learning a skilled reaching task (SRT), in rats performing reaching-like forelimb movement without learning (activity control task, ACT) and in rats that were trained in the operant but not the motor elements of the task (control group). Apart from M1, Arc expression was also assessed within the rostral motor area (RMA), primary somatosensory cortex (S1), striatum (ST) and cerebellum.~~

~~In SRT animals, *Arc* mRNA levels in M1 contralateral to the trained limb were 31% higher ipsilaterally ($p<0.001$), 31% higher than in the contralateral M1 of ACT animals ($p<0.001$) and 48% higher than in control animals ($p<0.001$). *Arc* mRNA expression in SRT was positively correlated with learning success between two sessions (r=0.52; p=0.026). For RMA, S1 and ST, no significant~~

differences in *Arc* mRNA expression were found between hemispheres or across behaviors. For cerebellum, only negligible low levels of *Arc* mRNA were observed. As *Arc* expression has been related to different forms of cellular plasticity, these findings suggest a link between M1 *Arc* expression and motor skill learning in rats.

**Key words**: **Arc, FISH, motor learning, motor cortex**

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# IIntroduction

While the process of motor skill learning depends on the interaction of different brain regions (e.g. namely sensorimotor cortex, (SM), basal ganglia, (BG) and cerebellum, (C; Hikosaka et al., 2002), evidence points to primary motor cortex (M1) as the structure where motor memory traces are formed. Skill acquisition requires protein synthesis within M1 and induces long lasting changes in M1 in synaptic strength (Rioult-Pedotti et al., 2000), in M1 possibly reflecting the storage mechanisms for motor memories (Kleim et al., 2003, Luft et al., 2004). However, Learning induces long lasting changes in M1 synaptic strength (Rioult-Pedotti et al., 2000). little is known about the genes and proteins that mediate theses processes.

In rats, the immediate-early gene (IEG) c-fos is expressed within M1 after beginning to training an acrobatic locomotor skill and, C-fos remains elevated when a performance plateau has been reached (Kleim et al., 1996). Recently, increased levels of Arc (activity-regulated cytoskeleton-associated protein), a protein coded by the IEG Arc (also known as the activity-regulated gene 3.1 Arg3.1) have been found in M1 of rats that trained precision reaching task with the contralateral forelimb (Hanlon et al., 2009). As this study focused on the

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effect of motor training on ~~slow wave activity an cortical~~ IEG expression during non-REM sleep, its an open question if ~~it did not reveal whether~~ Arc-induction was specific to learning or simply related to ~~a~~ activity, i.e. moving the forelimb more than usually.

As IEGs have been extensively studied within the hippocampal network, all knowledge summarized here was obtained from this system unless cited differently. ~~IEGs~~IEGs ~~-~~ typically are transcribed within few minutes after induction of long-term potentiation (LTP, Worley et al., 1993; Guzowski et al., 1999). In contrast to the IEG *c-fos*, an activity-induced transcription factor that controls the expression of other transcription factors, *Arc* is an "effector-IEG" ~~, that~~ that promotes~~induces the~~ transcription of proteins ~~directly related to cellular modifications~~ influencing~~such as changes in the~~ cytoskeleton or synaptic AMPA receptor trafficking (Bramham et al., 2008, Miyashita et al., 2008). These modifications are thought to mediate learning related ~~underly~~ cellular plasticity. Learning and experience-related transcription of *Arc* mRNA has been observed in various behavioral paradigms such as the Morris water maze task (Guzowski et al., 2000, Fletcher et al., 2006). In animals not subjected to learning paradigms, *Arc* is transcribed at very low levels. Upon excitatory synaptic activation Arc is expressed within minutes (Lyford et al., 1995) in an "all-or-nothing" fashion (Guzowski et al., 1999). Its induction is confined to neural assemblies associated with the encoding of information of specific behavioral experiences (Steward et al., 1998, Guzowski et al., 1999). After induction, *Arc* mRNA is transported into dendrites and accumulates at sites of synaptic

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activation where it is locally translated into proteins (Steward et al., 1998). Hence, Arc can be considered as a cellular marker of learning-related synaptic plasticity.

The objective here was to investigate, if ~~whether M1 *Arc* induction is specific for motor skill learning or whether it is related to motor activity in the absence of learning. Further, we investigated whether~~ Arc becomes ~~is~~ induced in M1 and other ~~other~~ brain regions related to motor learning in a ~~concerned with~~ learning-specific manner~~motor skill learning~~ and if~~whether~~ the degree of Arc induction is related to learning efficacy.

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# Material and Methods

## Animals

Adult male Long-Evan rats (8-10 weeks, 250-350 g, Centre d'Elevage R. Janvier, Le Genest-St. Isle, France) were used for all experiments. Animals were housed individually in a 12/12-hr light/dark cycle (light on: 8pm, off: 8am). Littermates were distributed equally among the groups of an experiment. All experiments were conducted in accordance with German and Swiss regulations and were approved either by the Animal Commission of the State of Baden-Württemberg or the Committee for Animal Experimentation of the Canton of Zürich.

## Behavioral conditions

Training sessions were performed at the beginning of the dark phase. Animals were food-restricted for 24 hr before the first training session. During training animals were kept slightly over their initial weight by providing 50 mg/kg of standard lab diet after each training session. Water was given *ad libitum*. The behavioral tasks were performed as previously described (Molina-Luna et al., 2008). The training cage was a 15 x 40 cm chamber (height 30 cm) with a vertical window (1 cm wide, 5 cm high, lower edge 2 cm above ground) in the front wall and a small light sensor in the rear wall (7 cm above ground).

Three different behavioral conditions were compared: a motor skill learning paradigm (skilled reaching task; SRT), ~~and~~ a paradigm requesting arm movements without motor learning (activity control task; ACT) and controls with the operant but without the motor elements (control group; CG). ~~Animals were killed after pre-training were used as a control.~~ These rats were exposed to the same training cage and had accessed a food pellet by tongue (pre-training). Because for technical reasons animals from the three groups could be evaluated in the same immunohistochemitry run, pairwise matching was performed between SRT/ACT and SRT/control~~trol~~ in two runs. Animals in the SRT/ACT or SRT/CG~~controls~~ pairings were trained for exactly the same amount of time.

As behavioural tasks were embedded in an operant conditioning paradigm, animals required a pre-training to operate the experimental setup properly, before being assigned to a particular experimental group. During this pre-training, animals learned to open the motorized sliding door that covered the front window by nose-poking the sensor in the rear. Opening the window gave access

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to one food pellet (45 mg, Bio-serve, Frenchtown, NJ, USA) located on a small horizontal board in a distance of 0.5 cm relative to the outside edge of the window. Thus, pellets could be retrieved . ~~During pre-training, pellets were retrieved~~ by tongue without utilization of the forepaw. Upon retrieval a pellet dispenser automatically replaced the pellet. Whereas SRT and ACT animals were pre-trained for five days, control animals were killed after two days of pre-training.

*Skilled reaching task (SRT):*

In SRT animals pre-training was followed by motor training that was initiated by removing the board and placing the pellet on a small vertical post 1.5 cm away from the window. In this position pellets were only retrievable by using the forelimb. Because the diameter of the post was approximately that of the pellet, the pellet was in an unstable position easily kicked off the post. Before the first skill training session, forelimb preference was determined. Then the pedestal was shifted to one side of the window to allow for reaching with the preferred limb only. To retrieve the pellet rats had to extend the forelimb towards the target, pronate, open the paw, grasp, and pull the forelimb back while supinating to bring the pellet towards the mouth (Whishaw and Pellis, 1990). Each reaching trial was ~~scored as "successful" (reach, grasp and retrieve) or "unsuccessful" (pellet~~ pushed off pedestal or dropped during retraction).

For the skilled-reaching task in male Long-Evans rats, motor learning seems to be especially effective during the second day of training as the highest increase in learning success occurs between sessions two and three (Buitrago et al.,

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2004). Regarding the intra-session learning curve at day two, the steepest increase in successful grasps can be found between trials 40 to 60 (Buitrago et al., 2004). To display expression of *Arc* mRNA at this particular sensitive time-point, animals were killed after ~~The first session (d1) consisted of 100 door openings (= trials), the second session (d2) consisted of only~~ 50 trials at day 2 whereas training day 1 consisted of 100 trials. ~~to focus on the time point when the averaged learning curve has its steepest course (Buitrago et al., 2004).~~ The improvement of reaching performance between sessions was defined as the difference of successful trials between training on day 2 (50 trials) and – to render the comparison valid – the first half (50 trials) of the training session on day 1. In case rats showed a lower performance at day 2 compared to day 1, negative values of learning rates were depicted.

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Activity control task (ACT)

The ACT consisted of extending the forelimb through the window to touch a sensor in 1.5 cm distance. If the sensor was touched, the investigator gave the rat a pellet directly into the mouth of the rat using forceps. Limb position during reaching in ACT was identical to SRT but no grasping or pellet retrieval was necessary.

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## Tissue preparation

~~*Arc* mRNA can be detected in the cytoplasm of neurons about 20 to 45 minutes after induction (Guzowski, 2002). The training session on day 2 lasted approximately 20 minutes.~~ Animals were killed 15 minutes after the second~~end~~ training~~of that~~ session ended. Animals were then deeply anesthetized (pentobarbital; 50 mg/kg i.p.; Kantonsapotheke Zurich, Switzerland) and perfused transcardially with PBS followed by 4% paraformaldehyde (PFA). All solutions used for animal dissection were prepared RNase-free. The brains were removed and kept for 24 hours in 4% PFA, then for 24 hours in 10% glycerol and finally for 1-2 days in 20% glycerol all at 4°C. Subsequently, brains were rapidly frozen in 2-methylbutane. Coronal sections (40µm) were prepared using a freezing/sliding microtome (Leica Microsystems GmbH, Wetzlar, Germany). For each animal, three brain sections containing the forelimb representation of M1 (3 mm ant. to 0.5 mm anterior to bregma), RMA (3.5 mm ant. to 1.5 mm anterior to bregma), S1 (1 mm ant. to 1.5 mm posterior to bregma) and striatum (2 mm anterior to 0.5 mm posterior to bregma) were collected, stereotactic coordinates were derived from Paxinos and Watson, 1998. The three sections were equally spaced (fixed distance of 600µm between subsequent slices) with a randomly chosen starting point, which was retained for matched behavioral pairings. ~~In principle, a systematic random sampling approach (random starting point, fixed distance of 600µm between subsequent slices was applied for selection of brain slices. However, to remain comparability between groups, similar starting points were used for matched pairs. For SRT and ACT animals, both hemispheres were sampled.~~ The hemisphere contralateral to the forelimb preferred for reaching will

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**Kommentar [M2]:** Strenggenommen hätte man dann eigentlich jeden 15. Schnitt verwenden sollen und nicht auf 3 Schnitte begrenzen.

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**Kommentar [M3]:** Würde man stereologisch auch nicht so machen.

Mein Vorschlag unten versucht die stereologischen Schwachpunkte etwas zu kaschieren.

**Kommentar [M4]:** The three sections were equally spaced (fixed distance of 600µm between subsequent slices) with a randomly chosen starting point, which was retained for matched behavioral pairings.

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be referred to as “contralateral hemisphere“ –(cSRT and cACT), the opposite hemisphere as ipsilateral (iSRT and iACT).

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## Arc probe generation

Riboprobes were generated from nearly full-length rat *Arc* cDNA inserted into pBluescript II SK plasmid (provided by Drs. J. Guzowski and P. Worley). Sense and antisense digoxigenin-labeled probes were transcribed from the linearized plasmid using DIG RNA Labeling Mix, and T3 or T7 RNA polymerases respectively (Stratagene, La Jolla, CA). Probes where then purified on mini Quick Spin RNA Columns. ~~To improve tissue penetration, probes were alkaline hydrolyzed for 30 minutes at 60°C.~~ Probe concentration was estimated by spotting serial dilutions of probe and DIG-labeled control RNA on membranes, immunodetection with anti-DIG Fab fragments conjugated to alkaline phosphatase, and colorization with nitro blue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate. All reagents were obtained from Roche Diagnostics, Mannheim, Germany unless indicated otherwise.

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## *In situ* hybridization immunohistochemistry

Fluorescent *in situ* hybridization was performed using a modified version of the protocol described by Wegenast-Braun et al., 2009, allowing for application in rats. Solutions used for in situ hybridization were prepared RNase-free. Sections were mounted onto slides (SuperFrostPlus; R. Langenbrinck Labor- und Medizintechnik, Teningen, Germany). If mounted sections were processed

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individually, differences in staining intensities could be a possible source of confounds. To overcome this problem, brain sections from different experimental groups were distributed in a balanced fashion, i.e. sections from each brain region derived from a SRT animal were mounted pairwise with their counterparts from the ACT or control group on the same slide. Aside from this rule, pairs of sections were distributed in a random order.

Mounted slides were dried for 1 hour at 30°C, and postfixed for 20 minutes in 4% paraformaldehyde in PBS at 4°C, followed by three washes in PBS. Sections were permeabilized with 0.3% Triton-X100 in PBS and 30 μg/ml proteinase K in Tris EDTA (TE) [10 mM Tris-HCl and 1 mM EDTA, pH 7.5] at 30°C with interleaved PBS washes. Proteinase K treatment was stopped by 0.2% glycine in PBS with 50 mM EDTA followed by two PBS washes. Tissue was then equilibrated in 0.1 M triethanolamine (TEA) and acetylated with 0.25% acetic anhydride in 0.1 M TEA. After three washes in 2x SSC [0.3 M NaCl and 0.03 M sodium citrate, pH adjusted to 7.0 with citric acid], sections were dehydrated through graded alcohols and defatted in chloroform. Tissue was rehydrated through graded alcohols and dried. For hybridization, the probe RNA was diluted to 100 ng/ml in hybridization buffer [50% deionized formamide, 2x SSC, 1 Denhardt's solution (1% bovine serum albumin, 1% polyvinylpyrolidone, and 1% Ficoll), 10% dextran sulfate, 0.5 mg/ml wheat germ tRNA, and 0.5 mg/ml salmon sperm DNA] and denatured at 80°C for 5 minutes before application to tissue. Sections were then sealed with a coverslip and incubated 16 to 20 hours at 59°C in a humid chamber. Coverslips were removed and slides were washed twice in

2x SSC/1 mM EDTA. Then, sections were treated with 10 µg/ml RNase A (Sigma-Aldrich, Steinheim, Germany) in TE/0.5 M NaCl and washed twice with 2x SSC/1 mM EDTA. Stringency washes were performed in 0.1x SSC/1 mM EDTA at 59°C for 1-2 hours and two times in 0.5 SSC at room temperature for 5 minutes. Endogenous peroxidase activity was quenched with 1% H2O2 in PBS, followed by subsequent washes in PBS, washing buffer [100 mM maleic acid, 150 mM sodium chloride, 0.3% Tween-20, pH adjusted to 7.5] and tris-buffered saline (TBS) (84 mM Tris-HCl, 16 mM Trisbase, and 154 mM NaCl). Sections were blocked with 10% bovine serum albumin in TBS and incubated with anti-DIG Fab fragments conjugated to horseradish peroxidase diluted 1:400 in 10% bovine serum albumin in TBS for 2 hours at 4°C for detection. After three washes with washing buffer, the conjugate was detected with Cyanine-3 Tyramide Working Solution (TSAPlus Fluorescence Systems, Perkin Elmer). Developed sections were washed with TE and PBS, counterstained with 4´6-diamidino-2-phenylindole (DAPI; Sigma-Aldrich) and allowed to dry before adding coverslips with VectaShield (Vector Laboratories, Burlingame, CA

~~).~~

## Confocal microscopy and data analysis

Regions of interests (ROIs) were identified by cortical cytoarchitecture: S1 could be easily identified due to prominent layer IV, M1 on the other hand by the absence of such a granular layer. RMA could be defined due to high neuronal

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density and a feathering of the strict layered order of cortex towards midline. Mosaic-iImages ~~of the particular ROIs~~ comprising the ROI ~~entire anatomic region of interest (e.g. M1)~~ were taken with a Zeiss LSM 510 META (Axiovert 200M) confocal microscope equipped with three lasers (488, 543 and 633 nm) using a Zeiss Plan-Neofluar 20x/0.5 air objective. Settings were kept constant for different imaging sessions. Laser powers were regularly measured with a PT 9610 laser power analyzer (Gigaherz-Optik, Puchheim, Germany) to control for changes in intensities. To avoid edge artifacts at the cut surfaces of the tissue, the ~~optical~~focal plane was set below the surface, well within the penetration margin of the in situ hybridization signal. ~~with the size~~The optical thickness ~~of~~ was set to 5.6 µm ~~was taken from the middle of the brain slices~~.

To avoid an oversampling by including *Arc* mRNA positive neurons of neighboring structures, the counting area (ROI) was set with a lateral security zone of 50µm apart from the microscopically defined border. RGB images were analyzed ~~offline~~ using ImageJ software (Cell counter plugin) by ~~chand-c~~ounting neurons within this marked area showing ~~-~~expression of *Arc* mRNA (Cy3) ~~within one region of interest~~. ~~–~~Training sessions on day 2 had a duration of approximately 20 minutes and animals were killed exactly 15 minutes after the end of the behavourial training. *Arc* mRNA is present in the cytoplasm of neurons 20 to 45 minutes after its induction (Guzowski, 2002), only cells with a clear cytoplasmic staining-pattern were counted to ensure that only the *Arc* mRNA expression induced by the recent training session was measured.

Although the sampling and counting strategy used here is in good accordance

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with stereological rules, due to the lower number of sections sampled for each subregion (3), we resigned to extrapolate a total number of stained neurons per region and decided to present an average number of activated neurons per counted section within a region. ~~Average values for number of activated neurons were summed across the three analyzed sections for each brain region.~~ Because the overall number of samples was large, two runs of *Arc* mRNA in situ hybridization were required (SRT animals n=6 + controls n=6; SRT animals n=12 + ACT animals n=12). To account for potential differences in effectiveness and intensity of Arc mRNA-staining between hybridization runs, the numbers of positive cells of ACT and control group were normalized to the average value of their respective SRT group. Statistica version 7.0 (StatSoft, Inc., Tulsa, OK, USA) software was used to perform ANOVA tests for each brain region. Group and hemisphere were entered as independent variables. The dependent variable was the normalized number of *Arc* mRNA-positive neurons. If the overall ANOVA was significant, Bonferroni post hoc tests were computed. The relationship between *Arc* expression and inter-session improvement was assessed by linear regression analysis. Numerical results are expressed as mean and ± SEM.

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**Kommentar [M8]:** Sind die SRT Tiere unabhängig, insgesamt also 18?

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**Kommentar [M9]:** Also different behavioral runs?

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**Kommentar [M10]:** Waren die Werte sehr unterschiedlich? Andernfalls könnte man sie sogar benennen?

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## Results

In M1 *Arc* expression was differentially affected by the type of training and the hemisphere (ispsilateral versus contralateral; $F_{4,60}$=33.7 p<0.001). Post-hoc analysis revealed that the contralateral (trained) hemisphere of SRT (cSRT) animals showed stronger of *Arc* mRNA expression when compared to the ipsilateral hemisphere (iSRT, had 69% of *Arc* mRNA positive neurons compared to cSRT; p<0.001), cACT (had 69% of *Arc* mRNA positive neurons compared to cSRT; p<0.001), iACT (had 66% of *Arc* mRNA positive neurons compared to cSRT; p<0.001) and control group (had 52% of *Arc* mRNA positive neurons compared to cSRT; p<0.001; **Fig. 1a**). The number of *Arc* mRNA positive neurons within M1 of the control animals was significantly smaller when compared to the iSRT (p=0.019) and cACT group (p=0.037; **Fig. 1a**). *Arc* mRNA positive neurons were observed within all cortical layers within M1 except layer I (**Fig. 1b** and **c**).

The number of *Arc* mRNA positive neurons within M1 of the cSRT group was positively correlated to the learning rate (R-value: 0.523, p=0.026; **Fig. 2**), i.e. magnitude of improvement in grasping performance (d1 vs. d2) is related to a

higher Arc expression in M1 contralateral to the trained paw. Furthermore, there is also a non-significant trend towards a correlation between *Arc* mRNA expression in M1 of the ipsilateral hemisphere (iSRT) and learning rate (R-value: 0.402, p=0.098).

For RMA ($F_{4,56}$= 1.0 p=0.394; **Fig. 3a**), S1 ($F_{4,49}$= 0.5, p=0.7; **Fig. 3b**) and ST ($F_{4,54}$= 1.258, p=0.298; **Fig 3c**), no significant differences in *Arc* mRNA expression could be detected across behaviors.The number of Arc RNA-positive neurons in cerebellum was very low in all conditions, and was not quantitatively analyzed.

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## Discussion

This study demonstrates that *Arc* is induced in M1 shortly after motor skill acquisition at a significantly higher level than following motor performance without related learning. The degree of *Arc* expression correlates with performance, i.e. how successfully the motor skill was acquired.

Activation of *Arc* in neurons has been studied in various learning and conditioning paradigms. For example, *Arc* is induced in the olfactory cortex after exposure to odorants (Zou et al., 2005) or in hippocampus after spatial exploratory behavior (Ramirez-Amaya et al., 2005, Fletcher et al., 2006). ~~Moreover, *Arc* is not only a marker of cellular activity related to learning but also seems to be essential for memory consolidation in hippocampus-dependent~~

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~~learning. Infusing *Arc* antisense desoxyribonuclein acids (ODNs) into the hippocampus impaired the formation of spatial memory in the water maze (Guzowski et al., 2000) and the retention performance in an inhibitory avoidance task (McIntyre et al., 2005). *Arc* knockout mice fail to generate long-lasting memory in implicit and explicit learning tasks (Plath et al., 2006).~~

Here, the expression of *Arc* induced by different learning paradigms was studied in brain regions associated with motor control. *Arc* expressing neurons could be frequently detected in all brain regions that were sampled (M1, RMA, S1 and ST) except in cerebellum. This confirms previous studies showing *Arc* induction in α-calcium-calmodulin kinase II (αCaKMII) positive neurons in hippocampus, neocortex or striatum (Vazdarjanova et al., 2006), whereas cerebellar Purkinje cells are known to show minimal expression (Smith-Hicks et al., 2010). RMA, S1 and ST showed no statistically significant differences in *Arc* expression between different learning conditions or hemispheres. *Arc* was significantly upregulated selectively within M1 contralateral to the trained paw (cSRT) as compared to the ipsilateral hemisphere (iSRT) or to M1 of ACT and control animals. The degree of *Arc* induction correlated with learning success, suggesting a mechanistic link (without proving causation). These findings give further support to the assumption that M1 is an area where motor memories are consolidated (Luft et al., 2004). ~~Previous studies showing that *Arc* inhibition by antisense desoxyribonuclein acids (ODNs) impaired memory formation in hippocampus-dependent learning paradigms (Guzowski et al., 2000, McIntyre et al., 2005, Plath et al., 2006) suggest that similar inactivation in M1 would also impair motor~~

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~~learning but further studies are necessary to prove this hypothesis.~~

Hanlon et al. (2009) reported Arc expression in layer V neurons of M1 after rats were trained in reaching (Hanlon et al., 2009). This study was focused on the effect of motor training on slow wave activity and cortical IEG expression during non-REM sleep. Because immunohistochemistry against Arc protein was used, the findings had to be interpreted with caution~~. Immunohistochemistry measures Arc protein induction that does not follow as predictable a time course following learning~~. In contrast to protein induction, ~~In contrast,~~ transcription~~production~~ and intracellular transport of *Arc* mRNA ~~, which was measured by FISH here,~~ ha~~ve~~s a well-defined time course (Guzowski et al., 1999, Guzowski, 2002) and, hence, can be unequivocally linked to the learning that occurred shortly before. By measuring cytoplasmic mRNA, we therefore ensured that only those neurons in which *Arc* was induced by the motor training were visualized. Also, Hanlon and colleagues (2009) did not study control groups and, hence, cannot demonstrate learning-specific Arc induction.

In contrast to the findings of Hanlon et al. we found *Arc* mRNA to be expressed across all cortical layers except layer I. *Arc* mRNA is translated locally at active synaptic sites (Steward et al., 1998). Its localization and accumulation there can be enhanced by activating the extracellular signal-regulated kinase (ERK; Huang et al., 2007). Thus, as ~~Furthermore, in rat dentate gyrus granule cells, ERK activation enhances the phosphorylation of the eucaryontic initiation factor 4E (eIF4E) resulting in an increased formation of translationally competent ribosomes and increased synthesis of Arc protein , (Richter and Sonenberg,~~

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2005, Panja et al., 2009). Thus, *Arc* mRNA trafficking ands well as its local translation are highly regulated processes that depend on local cofactors like activation of the ERK pathway. Therefore, it cannot be assumed that nuclear *Arc* mRNA expression and local synaptic Arc protein content are directly proportional.

Induction of *Arc* mRNA that occurs within minutes after a neuron became activated in relation to behavioral experience (Guzowski et al., 1999) seems to be an early step specifically tied to the encoding of a motor memory in M1. However, subsequent cascades of gene expression and maturation processes likely have to take place until the memory is fully consolidated (Luft and Buitrago, 2005). *Arc* mRNA trafficking, local translation of *Arc* mRNA into protein as well as the turnover of *Arc* mRNA is a strictly regulated process (Giorgi et al., 2007, Huang et al., 2007, Park et al., 2008, Bramham et al., 2010). Thus, the broad expression pattern of *Arc* mRNA comprising all cortical layers of M1 (except layer I) (**Fig. 1b** and **c**) may reflect an initial activation of neuronal populations in response to training. Later different processes may be required to selectively stabilize newly formed synapses (Xu et al., 2009) or strengthen specific synaptic connections that are functionally relevant.

Similar to *Arc* here, enhanced expression of the IEG *c-fos* in rat M1 occurred during acrobatic skill training (Kleim et al., 1996). As c-fos expression was highest during skill acquisition and decreased during maintenance phase, the learning-specificity of IEG expression in M1 is highly plausible. But besides the upregulation of *Arc* expression within M1 of the trained hemisphere in SRT rats, numbers of *Arc* mRNA positive cells within M1 ipsilateral to the trained paw in

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SRT and contralateral to the trained paw in the ACT group were also significantly higher than for controls. This most likely reflects the fact that ACT also involves some motor skill learning – although the skill is far less complex than SRT. Similarly, ACT rats show an increase of dendritic branching and spine density in M1 layer V neurons when compared to inactive control animals, but those plastic changes are less pronounced as compared to SRT rats (Wang et al., 2011). Increased levels of *Arc* mRNA in the ipsilateral M1 in SRT as well as the non-significant trend towards a correlation for *Arc* expression and learning success may reflect the contribution of the ipsilateral hemisphere to the learning process (Chen et al., 1997), however an unspecific bystander effect, e.g., through transcallosal activation, cannot be excluded.

That training-induced changes were confined to M1 and were not detectable within RMA, S1 and ST highlights the importance of M1 for motor learning. M1 has been proposed to be the site of storage of motor memory traces (Monfils et al., 2005). Protein synthesis in M1 is required for consolidation of a motor skill (Luft et al., 2004) and motor learning is accompanied by ~~various changes in M1:~~

~~a) At the network level, a transient enlargement of the forelimb representation can be observed after reach training (Kleim et al., 1998, Molina-Luna et al., 2008). The degree of enlargement correlates with performance improvements (Molina-Luna et al., 2008). b) At the cellular level, training stimulates the formation of novel synapses (Kleim et al., 2004) that become selectively preserved over time if they are functionally relevant (Xu et al., 2009). c) On the level of intercellular connectivity, motor training alters synaptic weights.~~

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~~Synapses of layer II/III horizontal connections become~~ synaptic ~~-~~strengthen~~ing ed~~ via LTP-like mechanisms~~ during motor learning~~ (Rioult-Pedotti et al., 1998, Rioult-Pedotti et al., 2000). It thus seems highly plausible that motor memories are stored within M1 circuitry.

~~The training-induced expression of *Arc* mRNA in M1 supports this view.~~ Through an interaction with dynamin and endophilin 2 and 3, Arc is the rate-limiting molecule in endocytosis of AMPA-type glutamate receptors at synaptic sites (Bramham et al., 2008). By regulating the homeostatic synaptic scaling of AMPA receptors (Shepherd et al., 2006), *Arc* is ideally suited to control synaptic strength and cellular excitability (Chowdhury et al., 2006, Rial Verde et al., 2006, Bramham et al., 2008). Moreover, Arc is an essential protein for LTP consolidation (Guzowski et al., 2000, Plath et al., 2006). Arc may not only regulate the translational machinery required for LTP consolidation (Bramham et al., 2010), by controlling F-actin polymerization it also modulates structural changes like the expansion of postsynaptic spines underlying late-phase LTP (Bourne and Harris, 2008). Such an expansion of postsynaptic spine width in combination with LTP in layer 1 horizontal connections has been also observed within M1 of rats that learned a reaching task (Harms et al., 2008).

~~Induction of *Arc* mRNA that occurs within minutes after a neuron became activated in relation to behavioral experience (Guzowski et al., 1999) seems to be an early step specifically tied to the encoding of a motor memory in M1. However, subsequent cascades of gene expression and maturation processes likely have to take place until the memory is fully consolidated (Luft and Buitrago,~~

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~~2005). *Arc* mRNA trafficking, local translation of *Arc* mRNA into protein as well as the turnover of *Arc* mRNA is a strictly regulated process (Giorgi et al., 2007, Huang et al., 2007, Park et al., 2008, Bramham et al., 2010). Thus, the broad expression pattern of *Arc* mRNA comprising all cortical layers of M1 (except layer I) (**Fig. 1b** and **c**) may reflect an initial activation of neuronal populations in response to training. Later different processes may be required to selectively stabilize newly formed synapses (Xu et al., 2009) or strengthen specific synaptic connections that are functionally relevant.~~

In summary, our findings suggest a mechanistic link between M1 *Arc* expression and motor skill learning in rats. As training-dependent *Arc* expression was confined to M1 therefore suggests the formation of motor memory traces in M1 neurons.

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## Figure legends

**Figure 1**. ***Arc* mRNA expression within M1.** (**A**) More *Arc* mRNA positive neurons were found in the hemisphere contralateral to the trained forelimb of

SRT animals (cSRT) as compared to the other groups (iSRT: 69%; cACT: 69%; iACT: 66%; control group: 52%; **: p<0.001). *: M1 of control animals (CG) show less *Arc* mRNA expression when compared to the iSRT and the cACT group (p<0.05). Error bars indicate SEM. **(B)** and **(C)**. Representative confocal images taken from primary motor cortex of different groups. *Arc* mRNA positive neurons are distributed across all cortical layers except layer I. Note: sections in B were processed in a different FISH cycle than those shown in C. Vertical bars indicate the borders of cortical layers. Scale bar: 150 µm.

**Figure 2**. **Relationship between Arc mRNA expression in M1 and learning success (between sessions1 and 2).** The number of *Arc* mRNA positive neurons in the cSRT group (n=18) is significantly correlated to the learning rate (R=0.523, p=0.0259; grey~~red~~ lines indicate the 95% confidence interval).

**Figure 3**. **Arc mRNA expression across different brain regions.** Neither for RMA (**A**; p=0.349), S1 (**B**; p=0.7) nor ST (**C**; p=0.298) statistically significant differences were found between groups). Error bars indicate SEM.

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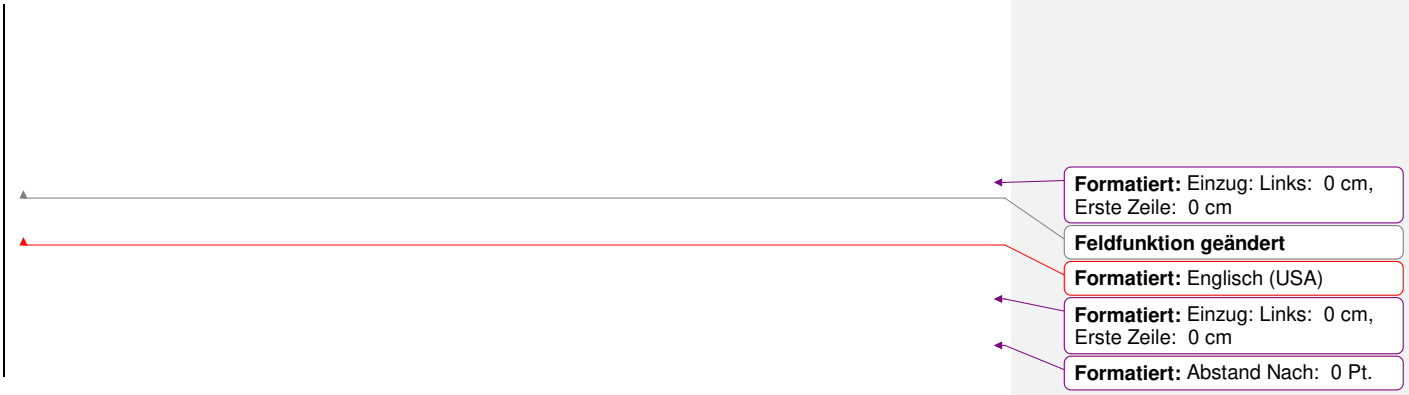
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